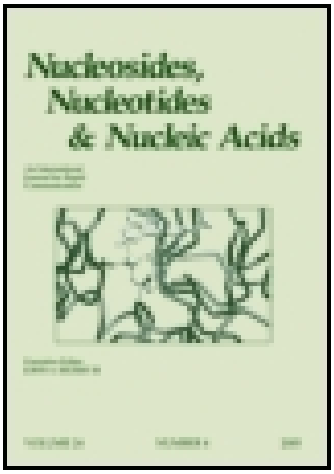

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Synthesis of [1-[2′,5′-bis-O-(t-Butyldimethylsilyl)-β- L-ribofuranosyl] thymine]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide) (L-TSAO-T)

Simon Ingate [a] , Ana San-Félix [a] , Erik De Clercq [b] , Jan Balzarini [b] & Maríia-José Camarasa [a]

[a] Instituto de Química Médica (C.S.I.C.), Juan de la Cierva , 3. 28006, Madrid, Spain

[b] Rega Institute for Medical Research, Katholieke Universiteit Leuven , B-3000, Leuven, Belgium

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NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 299-301 (1995)

SYNTHESIS OF [1-[2',5'-BIS-*O*-(*t*-BUTYLDIMETHYLSILYL)-β-L-RIBOFURANOSYL]THYMINE]-3'-SPIRO-5"-(4"-AMINO-1",2"-OXATHIOLE-2",2"-DIOXIDE) (L-TSAO-T)

Simon Ingate[1], Ana San-Félix[1], Erik De Clercq[2], Jan Balzarini[2], and María-José Camarasa*[1]

Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, 3. 28006 Madrid, Spain[1]
Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000, Leuven, Belgium[2]

Abstract: Derivatives of TSAO-T based upon pentofuranose sugars with the L-configuration have been prepared and evaluated as inhibitors of HIV-1 induced cytopathicity.

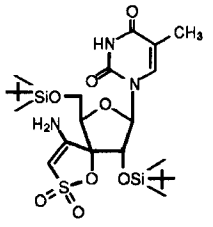
INTRODUCTION

Since the discovery that the TSAO family of compounds, the prototype of which is [1-[2',5'-Bis-*O*-(*t*-butyldimethylsilyl)-β-D-*ribo*-furanosyl]thymine]-3´-spiro-5"-(4"-amino-1", 2"-oxathiole-2",2"-dioxide) designated here as D-TSAO-T **1**,[1] are highly potent, specific HIV-1 reverse transcriptase inhibitors; many modifications of the basic structure have been studied.[2-5]

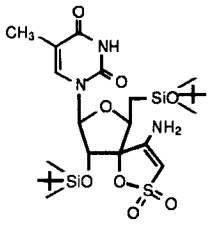
Some 2',3'-dideoxy-L-pyrimidine nucleosides such as β-L-ddC and (-)-2',3'-dideoxy-3'-thiacytidine [(-)-3TC] exhibit strong anti-HIV activity in cell culture and are targeted at the retroviral reverse transcriptase.[6,7] With this in mind and to compare its activity with D-TSAO-T **1**, the synthesis of the L-isomer of TSAO-T, henceforth known as L-TSAO-T **2**, was carried out.

Furthermore, studies on the effects of changing the nature of the protecting groups at the 2'-*O* and 5'-*O* positions on the antiviral activity [5] have shown the relative importance of the 5'-*O*-*t*-BDMS substituent. It was of particular interest to see if the position of this group was vital to the inhibitory function of TSAO-T. Since it was not known if a change in the configuration at the *C*-4 position would affect the accessability of the amino group at *C*-4" of the spiro moiety it was of importance to synthesise both the L-*arabino* **3** and L-

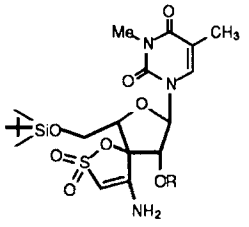
lyxo **4** isomers of TSAO-T. Thus, a synthetic route starting with L-*arabino*-thymine **8** was devised.



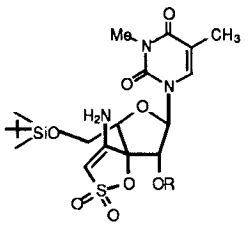
1 D-TSAO-T



2 L-TSAO-T



3 L-ara-TSAO-T



4 L-lyxo-TSAO-T

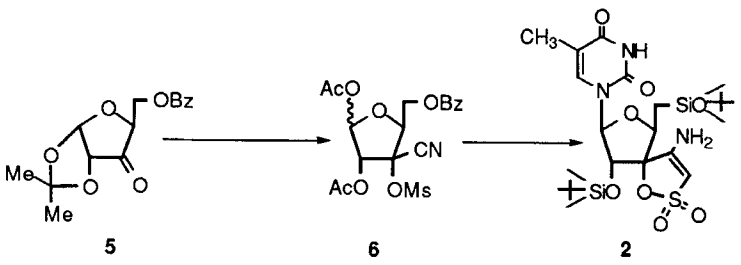
SYNTHESIS

(a) ***The synthesis of L-TSAO-T 2***

Following the procedure for the synthesis of **1**[1] the L-analogue **2** was synthesised from L-xylose via the key intermediates **5** and **6** (Scheme 1).

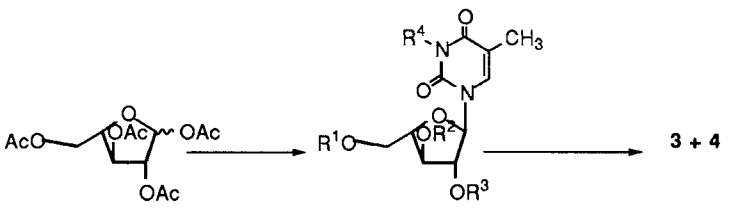
(b) ***The synthesis of L-arabino-TSAO-T 3 and L-lyxo-TSAO-T 4***

Beginning with L-*arabino*-furanose-1,2,3,5-tetraacetate **7**[8] (Scheme 2), glycosylation with persilylated thymine followed by deprotection yielded the nucleoside



5 **6** **2**

Scheme 1



8 $R^1=R^2=R^3=R^4=H$
9 $R^1=R^2$=tBDMS, R^3=Bn, R^4=Me
10 R^1=tBDMS, R^2=H, R^3=Bn, R^4=Me

Scheme 2

8. Silylation with *tert*-BDMSCl in pyridine gave a mixture of products, of which only one disubstituted isomer **9** was isolated (50% yield).

N-Methylation yielded **9** and 2'-*O*-benzylation gave **10**. The 3'-*O*-silyl group was removed selectively with tetrabutylammonium fluoride in dry acetone[9] to give **11**. Oxidation of **11** followed by cyanomesylate formation gave a mixture of the isomers which were ring closed with Cs_2CO_3 in CH_3CN to give the compounds **3** and **4**.

The compounds **1** to **4** have been tested for anti-HIV-1 inhibition in CEM and MT-4 cell lines, but none of the modified compounds (**2** to **4**) have shown significant activity at subtoxic concentrations.

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